REMARKS

Claims 1, 48, 53, 65-69, 78, 79, 82-84, 88-93, 95, 99-106, 108-111, 116, 117, 119-121, 123-126 and 128-177 are in this case. Claims 66, 68, 69, 82-84, 92, 104, 105, 110, 111, 116, 117, 119-121, 123-126 and 128-148 have been withdrawn from consideration as directed to a non-elected invention. This amendment cancels claims 1, 65, 67, 95 and 166 without prejudice. The amendment further cancels withdrawn claims 110, 111, 116, 117, 119-121, 123-126 and 128-148. On entrance of this amendment, claims 48, 53, 78,79, 88-93, 99-103, 108, 109 and 149-165 and 167-177 are under consideration. Withdrawn claims 82-84 and 104-106 remain in this case.

Sequence Listing

A Sequence listing amended to include reference to SEQ ID NO. 8 is submitted concurrently with this response. Also submitted is a Statement Under 37 C.F.R. §1.821-1.825 with respect to the Sequence Listing submitted.

Amendment to the Specification

The Abstract has been amended to reduce the number of words to fewer than 150. For the convenience of the Office, a replacement page 127 for the Abstract is attached to this submission. The replacement page does not contain new matter. The amendment of the Abstract does not add new matter to the application. A replacement page 127 is provided for the convenience of the Office. This amendment obviates the objection.

Page 55 line 13 has been amended to insert reference to "SEQ ID NO. 8" with reference to Structure 21 of Scheme 2.

Structures **20** and **21** of Scheme 2 have been amended. As stated on page 55 of the specification at lines 12-14, N-formyl peptide **21** is an exemplary SRE for N-formyl peptide **20.** For structure **20**, an "S" was omitted from the chemical

structure. For structure **21** the peptide label should be fMLPGGK. For structure **21**, the "S" of methionine (M) was omitted and the NH groups of the two glycines (G) were omitted. Structure **21** has also been amended to recite "SEQ ID NO. 8." A replacement page for Scheme 2, page 100, is submitted for the convenience of the Office. The amendments to the structures are fully supported in Scheme 2 of the parent application USSN 09/815,296 from which this application claims priority.

The amendments to the specification do not add new matter to the application.

Amendment to the Claims

Claim 1 has been cancelled without prejudice.

Withdrawn claims 110, 111, 116, 117, 119-121, 123-126 and 128-148 have been cancelled without prejudice. All of claims 110-148 which were directed to multivalent ligands are now cancelled as directed to a non-elected invention.

Claims 78 and 149 have been made independent and have been amended to contain the recitations of claim 1 and have been further amended to better clarify that the multivalent ligand comprises signal recognition elements that are bonded to a molecular scaffold.

Claims 48 and 53 have been amended to depend from claim 78.

Claim 95 is cancelled without prejudice. Claim 100 has been made independent reciting the limitations of cancelled claim 95.

Claim 99 has been amended to depend from claim 100.

Claims 93, 100 and 167 have been amended to replace ATRP with atom-transfer radical polymerization.

Claim 78 has been further amended to insert the definition of the abbreviations SRE, BRE and FE. Claim 108 has been amended to replace BRE with "bonding recognition element."

Claim 149 is amended to incorporate the limitations of claim 166.

Claim 166 is cancelled as redundant in view of the amendment of claim 149.

Claim 152 is amended to correct an obvious typographic error.

Rejections and Objections

The abstract of the disclosure was objected to as containing more than 150 words. The abstract has been amended to reduce the number of words to fewer than 150.

The disclosure is objected to for informalities. Compound **21** in Scheme2 is said to fall within the amino acid sequence rules and to require a sequence identifier number ("SEQ ID NO."). Scheme 2 has been amended to insert SEQ ID NO. 8.

A sequence listing (electronic version) is concurrently submitted herewith which includes SEQ ID NO. 8 based on Scheme 2 as amended. It is believed that the amendment to the specification and the submission of the Sequence Listing obviate the objection to the specification.

Claims 1, 48, 53, 65, 67, 78, 79, 88, 93, 95, 99,100,108,109, and 149-160, 166 and 167 are rejected under 35 U.S.C. § 112, second paragraph, as being

indefinite for certain recitations.

Claim 1, and its dependent claims, are rejected because of the recitation "and bonded to a molecular scaffold", because it is unclear as to whether it is the multivalent ligand or the at least one receptor that is bonded to the molecular scaffold. Claim 1 has been cancelled, but language from claim 1 has been retained in claim 78 and claim 149. The language retained has been amended to better clarify that the multivalent ligand comprises a plurality of signal recognition elements which are bonded to a molecular scaffold and that the signal recognition elements are recognized by at least one of the receptors.

Claims 67, 93, 100,166, and 167 and Claims 78, 79, 88 and 108 are rejected because they recite terms ATRP or SRE and RE, which are abbreviations. Claim 67 has been cancelled. Claims 93, 100, 166, and 167 have been amended to replace ATRP with atom-transfer radical polymerization. Claim 78 has been amended to insert the full terms for SRE, BRE and FE. It is believed that in view of the amendment of claim 78, further amendment of these terms in claims 79, and 88 is not required for clarity. Claim 108 has been amended to replace BRE with bonding recognition element.

The amendments are believed to obviate the rejections under 35 U.S.C. § 112, second paragraph.

Prior Art Rejections

Claims 1, 48, 53, 65, 89-91, 95, 99, 101-103, 106, 108, and 109 are rejected under 35 U.S.C. § 102(b) as being anticipated by Whitesides et al, WO 98/46270 A2. Claims 1, 65 and 95 have been canceled obviating the rejection with respect to these claims. Each of Claims 48 and 53 now depend from claim 78 which is believed to obviate its rejection. Claim 99 now depends from claim 100 which is believed to obviate its rejection. Claims 89-91 and 101-103, 106, 108 and 109 remain in this case. Applicants respectfully traverse the rejection with respect to these claims.

The Office Action states:

> Whitesides, throughout the publication and at p. 3, lines 11-24, p. 7, lines 24-31, p. 14, lines 1-9, p. 15, lines 20-31, teaches multivalent ligands on a polymeric backbone of the form Y-(A)n, where Y is a framework, A is a functional group, and n is an integer greater than 10, 50 or more, or about 100 or more and wherein the functional group that is a signal recognition is covalently bonded to the framework that is a molecular scaffold, such as a liposome; teaches at p. 32, lines 7-13, polyvalent presenters that include Sialyl Lex that bind leukocyte receptor sites including integrins and selectins and are elements involved in signal recognition, inducing intracellular and intercellular responses; teaches at p. 60, line 26-p.61, line 20 modulation of cell-cell interactions by polyvalent presenters, (which include multivalent ligands), whereby numerous cell-cell interactions can be promoted or inhibited, such as neutrophil attachment to endothelial cells during inflammation; teaches at Table 2, p. 62, line 4-p. 63, line 7, cell-cell interactions that include neutrophil, endothelial cells, T-cells, and the release of platelet granules; teaches at p. 87, lines 3-18, teaches cytokine production by replacing a stimulator cell in a cell-cell interaction that normally leads to cytokine secretion, e.g., the L-selectin ligands to simulate monocytes and macrophages to produce tumor necrosis factor; teaches at p. 96, line 1-p. 99 line 16, *in vitro* assays; at p. 97, line 31- p. 99, line 16, teaches cross-linking multivalent receptors on the cell by agglutinins to prevent the biological response of viral binding to the cell surface.
>
> Whitesides et al., at pp. 18-20, Table 1, disclose polymethacrylate polymers and subunits derived from maleic anhydride or malic acid. Whitesides et al, at p. 38, disclose "preactivation" methods comprising

succinimide compounds. Whitesides et al, at pp. 63-75 and Tables 3 and 4, disclose modulation of infection and teach receptors for pathogens. Whitesides et al, at pp. 131-138, Table 10, disclose agglutination assays comprising polyvalent polymers inhibiting the adhesion of ricins to erythrocytes.

Whitesides et al., at p. 24, teach functional groups for tracking by providing a label that can be detected, e.g., by fluorescent or radioactive tag. Whitesides et al., at p. 36, lines 9-22, teach solid supports, such as beads. Whitesides et al., at pp. 70-72, teach bacterial pathogens. Whitesides et al., at p. 30, line 23, teaches a Group A ligand that is abciximab, reading on an antibody and a Fab fragment.

Applicants do not necessarily agree with the Examiner's characterization of Whitesides et al.

Claim 89 is directed to a method for enhancing aggregation of biological particles which comprises providing a multivalent ligand complex which comprises a plurality of recognition elements which each induce aggregation of one or more of the biological particles and contacting the biological particles with the complex. Claims 90 and 91 depend from claim 89. The Office Action states that "Whitesides et al, at pp. 131-138, Table 10, disclose agglutination assays comprising polyvalent polymers inhibiting the adhesion of ricins to erythrocytes." The cited reference does not appear to teach or suggest enhancing aggregation of biological particles of any type employing multivalent ligands. This rejection should be withdrawn with respect to claims 89-91.

Claim 101 is directed to a method for generating an assembly of biological macromolecules or particles which comprises providing a multivalent ligand which comprises a molecular scaffold to which a plurality of binding recognition elements are attached which, in turn, bind to one or more biological macromolecules or biological particles wherein the number, density and spacing of recognition elements bonded to the molecular scaffold are controlled and

contacting the multivalent ligand with biological macromolecules or particles such that the recognition elements of the ligand bind to two or more biological macromolecules or biological particles. Claims 102, 103, 106, 108 and 109 all depend from claim 101. The Office Action refers to the reference as teaching "agglutination assays comprising polyvalent polymers inhibiting the adhesion of ricins to erythrocytes," and "cross-linking multivalent receptors on the cell by agglutinins to prevent the biological response of viral binding to the cell surface." The cited reference does not appear to disclose generation of assemblies as claimed in claim 101. Further there does not appear to be any teaching in the cited reference of controlling the number, density and spacing of recognition elements bonded to the molecular scaffold. Because the cited reference does not teach all the limitations of claim 101, this rejection should be withdrawn.

Claims 1, 48, 53, 65, 67,78,79,88-91,93,95, 99-103,106,108, and 109 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al, WO 98/46270 A2, and Brocchini et al, WO 01/18080 A1. Claims 1, 65, 67 and 95 have been cancelled obviating the rejection with respect to these claims. Claims 48, 53, 79, and 88 depend from claim 78. Claims 90, 91 and 93 depend from claim 89. Claim 99 depends from claim 100. Claims 102, 103, 106, 108 and 109 depend from claim 101. Applicants respectfully traverse this rejection with respect to the claims remaining in this case.

The Office Action states:

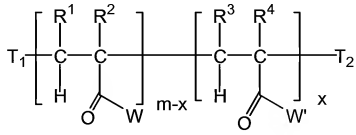
> Whitesides et al. is relied upon as above.
>
> Whitesides et al. does not teach a polymer scaffold that is an atom-transfer radical polymerization (ATRP) scaffold.
>
> Brocchini et al., WO 01/18080 A 1, throughout the publication and abstract, teach functionalized polymers, including polymeric multivalent ligands made by atom-transfer radical polymerization (ATRP). Brocchini et al, at pp.17-24, teach ATRP polymers having the formulae of claim 78.

It would have *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods for inducing biological response by multivalent ligands with a multivalent ligand polymer wherein the polymer scaffold that is an atom transfer radical polymerization (ATRP) scaffold.

One of ordinary skill in the art would have been motivated to use with a multivalent ligand polymer wherein the polymer scaffold that is an atom-transfer radical polymerization (ATRP) scaffold because Brocchini et al, at p. 1, lines 3-8, teach that such scaffolds are a class of polymer precursors with narrow molecular weight distribution and the production therefrom of physiologically soluble polymer therapeutics, functionalized polymers, pharmaceutical compositions and materials, all with similar molecular weight characteristics and a narrow molecular weight distribution.

With respect to claims 89 and 101, the deficiencies of Whitesides et al have been discussed above. Brocchini et al. do not teach or suggest a method for enhancing aggregation of biological particles or a method for generating an assembly of biological macromolecules or particles and do not cure the deficiencies of Whitesides et al. with respect to these claims or claims that depend therefrom. The rejection should be withdrawn with respect to all of claims 89-91 and 93 and 101-103, 106, 108 and 109.

Claim 78 is directed to a method for inducing a biological response in a biological system comprising one or more receptors which comprises the step of introducing into the biological system a multivalent ligand which comprises a plurality of signal recognition elements bonded to a molecular scaffold wherein the signal recognition elements are recognized by at least one of the receptors wherein the multivalent-ligand are polymers having the formula:



where:

m and x are integers and m is the number of monomers in the polymer;
W and W' are groups independently selected from –L-BRE, -L-FE, -L-SRE, a hydrogen or an organic group;
BRE is a binding recognition element;
FE is a functional element;
SRE is a signal recognition element;
L is an optional linker group;
T_{1-2} are polymer end groups which can include, among others, reactive or non-reactive groups and latent reactive groups; and
R^{1-4} can be the same or different groups and are most generally, independently of one another, hydrogen or any organic groups and where the polymeric ligand contains at least one W or W' that is a binding recognition element or a signal recognition element.

Whitesides et al. does not teach a polymer scaffold that is an atom-transfer radical polymerization (ATRP) scaffold and does not teach a polymer scaffold that is an ATRP scaffold as in claim 78. Additionally, Whitesides et al. does not teach or suggest that a multivalent ligand having the specific polymeric structure as claimed in claim 78 will function for any method of induction or inhibition of a biological response.

Applicants make no admission that Brocchini et al. is properly considered available as prior art to the claims in this rejection.

Brocchini et al. teach certain ATRP polymers apparently for use for therapeutic delivery of bioactive agents such as drugs, peptides and proteins. It appears that these polymers are intended to release the bioactive species. (see page 2, line 29) after uptake into cells. There is no teaching or suggestion in Brocchini et al. that the ATRP polymers with attached biological species will exhibit any biological activity while attached to the polymer. Thus, Brocchini et al. does not

cure the deficiencies of Whiteside et al. with respect to multivalent ligands as claimed in claim 78. Neither Whiteside et al. alone or in combination with Brocchini et al. provide one of ordinary skill in the art any reasonable expectation of success with respect to the use of the ATRP polymer as a scaffold for ligands which maintain biological function when attached to the polymer. In the absence of such a reasonable expectation of success, it would not be obvious to one of ordinary skill in the art to employ ATRP polymers in a method as claimed in claim 78. This rejection should be withdrawn with respect to all of claims 78, 79, 88 , 48 and 53.

Claim 100 is directed to A method for inducing or enhancing induction of a cellular response which comprises the steps of: forming a multivalent ligand which comprises a plurality of signal recognition elements which individually bind to the cell and induce the cellular response and contacting the cells with the multivalent ligand in an amount sufficient to enhance the cellular response, wherein the multivalent ligand is a ROMP-derived polymer or an atom-transfer radical polymerization polymer. This claim requires that the signal recognition elements "individually bind to the cell" and enhance cellular response. Claim 99 depends from claim 100.

Whitesides et al. does not teach a polymer scaffold that is an atom-transfer radical polymerization (ATRP) scaffold as in claim 100. Additionally, Whitesides et al. does not teach or suggest that a multivalent ligand that is an atom-transfer radical polymerization (ATRP) scaffold will function to allow signal recognition elements attached to the scaffold to individually bind to the cell and induce the cellular response as claimed in claim 100. While Brocchini et al. teach certain ATRP polymers for therapeutic delivery of certain bioactive agents the polymers are intended to release the bioactive species. (see page 2, line 29) after uptake into cells. There is no teaching or suggestion in Brocchini et al. that the ATRP polymers with attached biological species will exhibit any biological activity while

attached to the polymer. While Brocchini et al. suggest that the polymer will be taken up by the cells, there is no teaching or suggestion that signal recognition element attached to such a polymer will individually bind to cells to induce any biological response. Brocchini et al. does not cure the deficiencies of Whiteside et al. with respect to multivalent ligands as claimed in claim 100. Neither Whiteside et al. alone or in combination with Brocchini et al. provide one of ordinary skill in the art any reasonable expectation of success with respect to the use of the ATRP polymer as a scaffold for ligands which can individually bind to a cell when attached to the polymer as required by claim 100. In the absence of such a reasonable expectation of success, it would not be obvious to one of ordinary skill in the art to employ ATRP polymers in a method as claimed in claim 100. This rejection should be withdrawn with respect to claims 99 and 100.

Claims 149-177 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitesides et al., WO *98/46270* A2, and Brocchini et al., WO *01/18080* A1, as applied to claims 1, 48, 53, 65, 67,78,79,88-91,93,95,99-103, 106, 108, and 109 above, and further in view of Taylor et al., WO *03/007971* A1. Claim 149 has been amended to recite "wherein the polymer is an ATRP polymer or a ROMP polymer." Claim 166 has been cancelled. Applicants respectfully traverse the rejection with respect to claim 149 as amended and claims 150-165 and 167-177.

The Office Action states:

> Whitesides et al., WO *98/46270* A2, and Brocchini et al., WO *01/18080* A1, are relied upon as above.
>
> Neither of Whitesides et al. or Brocchini et al., WO *01/18080* A1, teach methods comprising ligand polymers comprising immune adherence, CR1 and Fab' fragments.
>
> Taylor et al., WO *03/007971* A1, throughout the publication and abstract, and at pp. 1-2, teach heteropolymer complexes comprising

antibodies specific for CR1 receptor in methods based upon the phenomena of immune adherence. Taylor et al., at p. 21, teach Fab' antibody fragments specific for CR1. Taylor et al., at p. 26, teach crosslinking antibodies using maleimide functional groups.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to combine methods of inducing biological response by multivalent ligands that bind to receptors, with methods comprising ligand polymers comprising immune adherence, CR and Fab' fragments.

One of ordinary skill in the art would have been motivated to use methods comprising ligand polymers comprising immune adherence, CR1 and Fab' fragments because Taylor et al., at pp. 5-9, teach the use of antibodies against CR1 expressed on erythrocytes in primates can dramatically affect the efficiency of the complex to clear pathogens or immunogens or antigens that bind to CR1, and because Taylor teach the use of such methods for detecting the presence of an antigen or pathogen in a mammal.

Applicants make no admission that Taylor et al. is properly considered available as prior art with respect to the claims that have been rejected.

Claim 149 is directed to a method for inducing a biological response in a biological system comprising one or more receptors which comprises the step of introducing into the biological system a multivalent ligand which comprises a plurality of signal recognition elements bonded to a molecular scaffold wherein the signal recognition elements are recognized by at least one of the receptors wherein the biological response is immune adherence and the biological system comprises erythrocytes and wherein the polymer is an ATRP polymer or a ROMP polymer. Claims 150-165 and 167-177 depend from claim 149.

The Office Action states that "(n)either of Whitesides et al. or Brocchini et al teach methods comprising ligand polymers comprising immune adherence, CR1 and Fab' fragments. Further, neither of Whitesides et al. or Brocchini et al. teach or suggest that multivalent ligands comprising signal recognition elements such

as CR1 and Fab' fragments attached to a molecular scaffold, such as an ATRP or ROMP polymer, will function for immune adherence in a biological system comprising erythrocytes as is claimed in claim 149.

Taylor et al. may teach heteropolymer complexes comprising antibodies specific for CR1 receptor in methods based upon the phenomena of immune adherence as well as Fab' antibody fragments specific for CR1. Taylor et al., at p. 26, appear to teach crosslinking antibodies. Taylor et al. does not however teach multivalent ligands having ROMP or ATRP scaffolds with attached signal recognition elements, such as CR1 and Fab' antibody fragments and further does not teach that such multivalent ligands will function for immune adherence in a biological system comprising erythrocytes. Thus, Taylor et al. does not cure the deficiencies of Whitesides et al. and Brocchini et al. with respect to the invention as claimed in claim 149.

None of Whiteside et al., Brocchini et al. or Taylor et al., alone or in combination, provide one of ordinary skill in the art any reasonable expectation of success with respect to the use of a ROMP or ATRP polymer as a scaffold for ligands which function for immune clearance in a biological system comprising erythrocytes as claimed in claim 149. Thus, this rejection should be withdrawn with respect to claims 149-165 and 167 to 177.

In view of all the foregoing the rejections should be withdrawn and the claims remaining in this case should be considered free of the prior art.

Claims 1, 48, 53,65,89-91,95,99,101-103,108, and 109 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 17, 21-23, 28-30,41-43,59-61,63-65,68-74,89-92,140-148, 150, and 156-163 of copending Application No. 09/815,296. Although the conflicting claims are not identical, they are not patentably distinct from each other.

U.S. application 09/815,296 has been abandoned. Abandonment of the '296 application obviates this rejection.

Applicants inform the Examiner that U.S. application 11/777,455 filed July 13, 2007 claims the benefit of U.S. application 09/815,296. No claims have been allowed in U.S. application 11/777,455. It is premature to argue a rejection based on an application in which no claims have been allowed.

Conclusion

Applicants respectfully request reconsideration of the claims. This response is accompanied by a Petition for Extension of Time of 3 Months. No fees for excess claims are believed to be due. The fees for this submission (petition fees of $525.00) are intended to be paid on EFS filing of this response. If the fees are not paid or the fees paid are incorrect, please credit any overpayment or deduct any deficiency from deposit account 07-1969.

Respectfully submitted,

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